

REMARKS

This Reply is responsive to the Office Action dated August 6, 2002. Reconsideration of the claimed subject matter in view of the amendments and remarks submitted herein is respectfully requested pursuant to 37 CFR §1.116.

The claims are amended in accord with the election of the embodiment of the invention in which dopamine cells are derived from a cloned ungulate produced by somatic cell nuclear transfer techniques and are transplanted into a patient to treat Parkinson's disease or a Parkinson's-type disease. As described in the specification, and in accord with the limitations of claims 15 and 55, the cloned dopamine cells for transplantation may be genetically modified. Claim 33 is amended to recite a fetal dopamine cell line having the limitation that it is derived from genetically modified differentiated fetal dopamine neuronal cells having proliferative life-span of freshly isolated fetal neuronal cells, support for which is found in Example 7. No new matter is added by the amendment.

Rejection of the claims under 35 U.S.C. §112, first paragraph:

Claims 1-6, 15-17, and 47-54 were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for methods of treatment by interspecies transplantation, or for treatment of any disease other than Parkinson's disease. The claims are allegedly not enabled because the specification does not provide guidance for: (a) preventing hyperacute immune rejection or otherwise maintaining the viability of the transplanted cells; (b) obtaining long-term expression of a therapeutic transgene in the transplanted cells; (c) obtaining cells for xenotransplantation when the cells to be isolated, expanded and transplanted are not rapidly dividing cells in the cloned donor ungulate animal; and (d) inducing stable differentiation of stem cells into dopamine-producing neuronal cells for treating Parkinson's disease. The examiner notes that the specification demonstrates that the invention provided temporary therapeutic benefit to experimental animals in an animal model for Parkinson's disease, but questions the value of a therapeutic method that "merely" treats a disease but does "not have a therapeutic outcome."

The Examiner is applying too stringent a standard in requiring that the claimed method provide a complete cure for Parkinson's disease. The present application describes results obtained in an experimental animal model for Parkinson's disease that are generally

accepted by those skilled in the art as being correlated with successful treatment in human and non-human patients suffering from Parkinson's disease and Parkinson's-type disease. It is recognized by persons skilled in the art of medical treatment that successful treatment of a disease can be effected by a method that only provides transient therapeutic benefit. For example, many successful treatments for cancer only provide temporary remission of the disease, and the patients must be subjected to additional therapy when the cancer returns. to the use of the cloned cells for transplantation into other mammals. It is also recognized by persons skilled in the art of medical treatment that a disease requiring transplantation therapy can be treated successfully even when the cells that are transplanted elicit an immune rejection response that must be inhibited by administration of immunosuppressive drugs. In fact, immunosuppressive drugs are routinely administered to transplant recipients to inhibit an immune rejection response and prolong the life of their transplant. The specification also teaches that the claimed method is uniquely suited to permitting one to perform extensive genetic modification of the cells to be transplanted, because somatic donor cells such as fibroblasts can be cultured in vitro for the extended periods of time required to perform complex genetic manipulations, e.g., by homologous recombination; and then can be "rejuvenated" to have a restored or enhanced proliferative life-span by the nuclear transfer cloning procedure. It is well within the skill of persons in the art to follow the teachings of the specification and perform genetic modifications in cultured ungulate cells that knock out the principal genes encoding the proteins responsible for eliciting an immune rejection response against the cells in a xenotransplant recipient. For example, 1,3-galactose epitopes found on the cell surfaces of almost all non-primate mammals are the major xenoantigens causing hyperacute rejection and acute vascular rejection in xenotransplantation of ungulate cells into humans (see Galali et al., 1994). Phelps et al. recently described successful production of cloned, α 1,3-galactosyltransferase-deficient pigs by using somatic cell nuclear transfer methods similar to the methods described in the present application (Science, 2003, 299:411-414; and Nature Biotechnology, 2002, 20:251-255, copies attached). Using similar methods, expression of genes encoding other ungulate proteins, such as MHC proteins, that contribute to immune rejection of a xenotransplant can also be knocked out. For example, porcine MHC class II proteins are reported to stimulate human CD4+ T cells (Yun et al., Transplantation, 2000, 15:940-944); and Veng et al. report that MHC-deficient murine

neuronal cells survive significantly longer in a xenotransplant than do wild type cells (Cell Transplant, 2002, 11:5-16, eabstract attached). A claimed therapeutic method need not satisfy all of the safety requirements of the Food and Drug Agency in order to comply with the enablement requirements of 35 U.S.C. 112, first paragraph. The claimed invention is a significant advance in the art. The invention provides a method for providing cells suitable for transplant to successfully treat Parkinson's disease, even if the benefits of the treatment are not permanent, and immunosuppression is required. Persons of skill in the art can make and use the invention successfully without having to perform undue experimentation. Accordingly, the Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, for non-enablement be withdrawn.

Rejection of claims under 35 U.S.C. §112, second paragraph:

Claims 18-25 were rejected under 35 U.S.C. §112, second paragraph, because the recitation of a "cloned cell line grown and maintained in a cloned bovine" was regarded as being indefinite. Claim 18 is amended so that the objected-to phrase is no longer present in the claim. Withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejection of the claims under 35 U.S.C. §102(b) and/or (e):

Claims 18-25 were rejected under 35 U.S.C. §102(b) as being anticipated by Sims et al. (1993). Claim 18 is amended to recites a cloned dopamine cell line derived from a cell of a cloned bovine having a genotype identical to that of a prior-existing fetal or adult bovine that was not the product of nuclear transfer techniques. The claimed cell line is derived from a clone of a prior-existing fetal or adult bovine; it is not derived from cells of an embryo produced by fertilization of an oocyte by a sperm. Sims et al. describe making culturing inner cell mass cells from embryos produced by in vitro fertilization to produce cloned ES cell lines. The cellular phenotypes that can be generated from the cloned ES cell lines produced by the method described by Sims et al. are unpredictable, because the embryos from which they are derived were created by the union of gametes having genetic information that is randomly rearranged by genetic recombination. In contrast, the cells of the claimed invention have the genotype of a pre-existing fetal or adult animal, so their cellular

phenotypes can be characterized and selected for useful properties; for example, production of above-average levels of dopamine, rapid growth in cell culture, or reduced capacity to elicit an immune rejection response. Accordingly, the claimed cell line is inherently distinct from cells produced by the method described by Sims et al., and withdrawal of the rejection under 35 U.S.C. §102 (b) is respectfully requested.

Claims 33-35 were rejected under 35 U.S.C. §102(b) as being anticipated by Huffaker et al. (1989); and claims 33-35 and 55 were rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,294,383 B1 (Isacson et al.).

Claims 33-35 and 55 recite a fetal dopamine-producing neuronal cell line that, like the cells of amended claim 18, are obtained by a method comprising cloning by nuclear transfer, using a nuclear donor cell from a fetal or adult ungulate. Huffaker et al. describe isolating dopamine-producing neuronal cells from fetal pigs produced by sexual reproduction (p. 330). Isacson et al. describe cells that are genetically modified *in vitro* prior to transplantation, or *in vivo* after transplantation (bridging cols. 23-24). Neither Huffaker et al. nor Isacson et al. describe a cell line having the inherent properties of the claimed cells, which arise out of their being cloned by nuclear transfer, which restores the proliferative life-span of the genetically modified nuclear donor cells. As a result, the claimd cells are distinct from the cells of the prior art. They are distinct from the cells of Huffaker et al. in being genetically modified, and they are distinct from the cells described by Isacson et al., because they are derived from genetically modified differentiated fetal dopamine neuronal cells having proliferative life-span of freshly isolated fetal neuronal cells. Genetic modification of cells *in vitro* by the methods described in Isacson et al. requires extended cell culture that results in reduction in the cells' proliferative life-span. The genetically modified cells of the present invention are derived from a cloned ungulate produced by somatic cell nuclear transfer, and have rejuvenated or enhanced proliferative life-span, and so are distinct from the cells of obtained by the prior art methods. In view of the above, withdrawal of the rejections under 35 U.S.C. §102(b) and (e) is respectfully requested.

Applicants appreciate the Examiner's indication that claims 1-6, 15-17, and 47-54 are free of the prior art.

The above remarks are fully responsive to the Office Action. If there are any issues remaining that need to be resolved, the Examiner is respectfully requested to contact the undersigned so that allowance of this application can be expedited.

Respectfully submitted,

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APPENDIX: AMENDED CLAIMS MARKED TO SHOW CHANGES MADE

Claims 1, 6, 15, 16, 18, 19, 25, 33, and 47 are amended as shown below:

1. (Amended) A method of treating a patient with Parkinson's disease or a Parkinson's-type disease [in need of cell or tissue transplantation] comprising administering to or transplanting into said patient [at least one cell or tissue] a therapeutically effective amount of dopamine cells obtained from a cloned ungulate [animal or embryo].

6. (Amended) The method of Claim 5, wherein said [at least one] cells [is a] are fetal dopamine neuronal cells[, and said cell transplantation therapy is effected to treat Parkinson's disease or a Parkinsonian-type disease].

15. (Amended) A method of treating a patient with Parkinson's disease or a Parkinson's-type disease comprising administering to or transplanting into said [a] patient [in need of such treatment with] a therapeutically effective amount of [a] cloned, transgenic fetal dopamine cells obtained from a cloned ungulate.

16. (Amended) A method of treating a patient with Parkinson's disease or a Parkinson's-type disease [in need of such treatment with] comprising administering to or transplanting into said [a] patient [in need of such treatment with] a therapeutically effective amount of cloned fetal dopamine neuronal cells obtained by [the following] a method comprising:

- (i) inserting a differentiated donor [ungulate] cell or cell nucleus from an ungulate embryo, fetus or adult into an enucleated [animal] ungulate oocyte under conditions suitable for the formation of a nuclear transfer (NT) unit;
- (ii) activating the nuclear transfer unit;
- (iii) culturing said activated nuclear transfer unit past the embryonic stage until blastocysts are formed;
- (iv) transferring blastocysts into a recipient female [animal] ungulate to allow development of a fetus; and
- (v) isolating differentiated fetal dopamine neuronal cells from said fetus,

wherein said fetal dopamine cell line has a genotype identical to that of a prior-existing differentiated embryo, fetus or adult ungulate that was not created by nuclear transfer techniques.

18. (Amended) A cloned dopamine cell line [grown and maintained in an *in vivo* environment, wherein said *in vivo* environment is] derived from a cell of a cloned bovine having a genotype identical to that of a prior-existing fetal or adult bovine that was not the product of nuclear transfer techniques.

19. (Amended) The cell line of Claim 18, wherein [said cell line and] said cloned bovine [have the identical] has a genotype identical to that of a [as another] prior-existing [embryonic,] fetal [or adult] bovine that was not the product of nuclear transfer techniques.

25. (Amended) The differentiated cell line of Claim 22, wherein said cell line is a line of dopamine neuronal cells.

33. (Amended) A genetically modified fetal dopamine neuronal cell line obtained by a method comprising:

- (vi) inserting a differentiated donor [ungulate] cell or cell nucleus from an ungulate embryo, fetus or adult into an enucleated [animal] ungulate oocyte under conditions suitable for the formation of a nuclear transfer (NT) unit; wherein said donor cell or cell nucleus is genetically modified;
- (vii) activating the nuclear transfer unit;
- (viii) culturing said activated nuclear transfer unit past the embryonic stage until blastocysts are formed;
- (ix) transferring blastocysts into a recipient female [animal] ungulate to allow development of a fetus; and
- (x) isolating genetically modified differentiated fetal dopamine neuronal cells from said fetus,

wherein said fetal dopamine cell line [has a genotype identical to that of a prior-existing differentiated embryo, fetus or adult ungulate that was not created by nuclear transfer techniques] is derived from genetically modified differentiated fetal

dopamine neuronal cells having proliferative life-span of freshly isolated fetal neuronal cells.

47. (Amended) A method of using an ungulate fetal dopamine neuronal [the] cell line [of Claim 33,] as a continuous and genetically identical source for transplantation purposes, comprising administering cells of said cell line to a patient with Parkinson's disease or a Parkinson[ian]s-type disease,

wherein said cell line is obtained by a method comprising:

- (i) inserting a differentiated donor cell or cell nucleus from an ungulate embryo, fetus or adult into an enucleated ungulate oocyte under conditions suitable for the formation of a nuclear transfer (NT) unit;
- (ii) activating the nuclear transfer unit;
- (iii) culturing said activated nuclear transfer unit past the embryonic stage until blastocysts are formed;
- (iv) transferring blastocysts into a recipient female ungulate to allow development of a fetus; and
- (v) isolating differentiated fetal dopamine neuronal cells from said fetus, wherein said fetal dopamine cell line has a genotype identical to that of a prior-existing differentiated ungulate embryo, fetus or adult that was not created by nuclear transfer techniques.